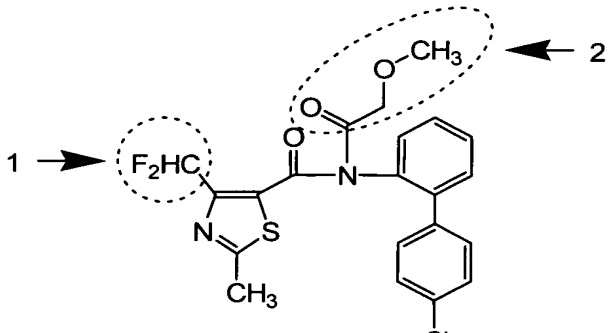
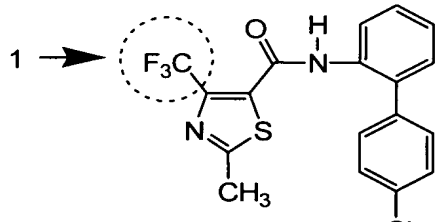
REMARKS

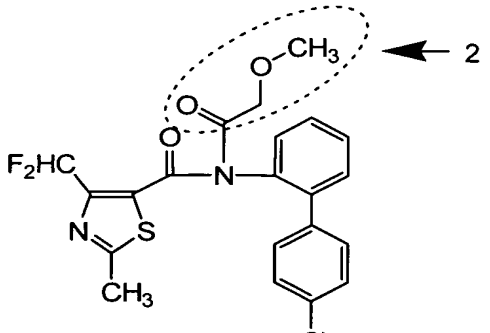
Applicants assume, based on statements in the Office Action at page 3 and elsewhere, that the comparison experiments described in the previously presented Declaration under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann are now correctly understood as comparing a single compound according to their invention (i.e., the compound of Applicants' Ex. 9) with two specific prior art compounds, namely the compound of Example 4.32 of WO 2002/059086 (and Example 4.31 of its counterpart application US 2004/0138265) and the compound of Example 21 of CA 2,474,902 (and its counterpart U.S. Application Serial No. 10/502,994, now published as US 2005/0124815). The formulas of these compounds can be represented by the following formulas (with key points of comparison shown with numbered arrows for each comparison set):



Applicants' Ex. 9



WO 2002/059086

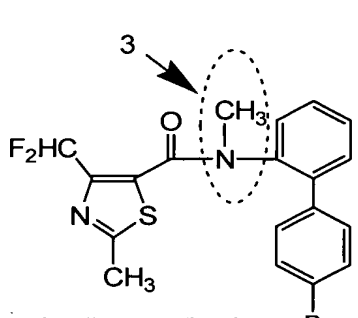


CA 2,474,902 &
S/N 10/502,994

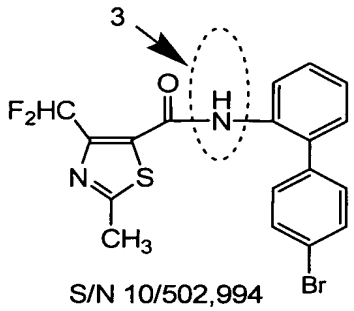
The data in Dr. Wachendorff-Neumann's Declaration show that (1) an inventive compound having a difluoromethyl substituent on the thiazole moiety is superior to a known comparison compound having a trifluoromethyl substituent and (2) an inventive compound having an N-substituted bridging amide nitrogen atom is

superior to a known comparative compound having an unsubstituted bridging amide nitrogen atom.

Notwithstanding the apparent acceptance of this Declaration for what it represents, the present Office Action states that the data presented in that Declaration are not commensurate in scope with Applicants' claims, with specific reference to certain other prior art compounds in the obviousness rejection discussed below that could have been tested. Applicants have therefore conducted additional comparison experiments using compounds referred to in the Office Action at page 5 (obviousness-type double patenting rejection) and page 9 (obviousness rejection as it relates to CA 2,474,902 ("Elbe et al")), namely the compounds of Example 6 according to their invention and Example 2 according to the copending '994 application and its counterpart CA 2,474,902. The formulas of these compounds can be represented as follows (with the key point of comparison again shown with numbered arrows):



Applicants' Ex. 6



S/N 10/502,994
& CA 2,474,902

The results of the experiments provided in the enclosed new Declaration under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann show – as will be discussed below – the superiority of Applicants' inventive compound. In fact, in a test for systemic efficacy against *Sphaerotheca fuliginea*, Applicants' inventive compound exhibited an efficacy of 100% at an application rate at which the known comparative compound exhibited no activity at all.

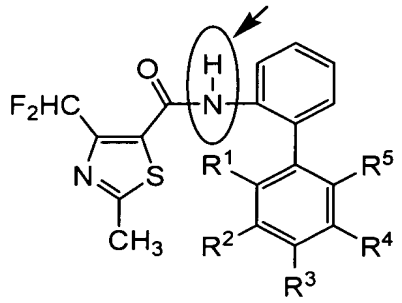
Allowable Subject Matter

Applicants again gratefully acknowledge the indication in the Office Action that Claims 26 and 28 stand objected to as being dependent upon a rejected base claim but would be allowable if rewritten in proper independent form. Applicants, however, maintain that all pending claims, including the base claim, are allowable as written and thus have not amended Claims 26 and 28 as kindly suggested.

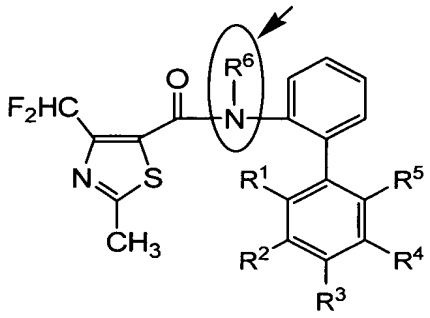
Double Patenting Rejection

Claims 18-25, 29, and 31-33 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 22-33 and 35-37 of copending application Serial No. 10/502,994. Applicants again respectfully traverse.

As Applicants have fully discussed in previous Amendments, the '994 application (as well as its Canadian counterpart CA 2,474,902) is directed to carboxamides of the formula



in which the bridging amide group is always unsubstituted (as shown by an oval and arrow), whereas Applicants claim carboxamides in which the bridging amide group must be N-substituted as shown below in formula (I) by the oval and arrow



(I)

The Office Action at pages 4-5, however, continues to rely on the Patent Office Board of Appeals decision *Ex parte Bluestone*, 135 U.S.P.Q. 199 (P.O.B.A. 1961), to support its assertion that substitution at the bridging amide nitrogen atom is obvious. The Board in that decision first noted that the examiner had found an N-methyl substituted compound to be unpatentable over the unsubstituted compound "in the absence of any showing of unexpected results" (see 135 U.S.P.Q. at 200, left column (emphasis added)) and further noted that "[t]here seems to have been no denial of the fungicidal equivalency of the alkyl and hydrogen N-substituted compounds" (see 135 U.S.P.Q. at 200, right column (emphasis added)). Here, in

contrast, Applicants have not only denied the equivalency of substituted and unsubstituted compounds, they have presented experimental evidence showing that such compounds are in fact not equivalent.

More specifically, Applicants' comparison experiments discussed above show that N-substituted compounds of their invention are superior to the unsubstituted counterparts. First, as has already been discussed in Applicants' previous Amendment dated August 28, 2007, Dr. Wachendorff-Neumann's first Declaration shows that the representative N-acylated compound of Applicants' Example 9 (as shown above) exhibited unexpectedly enhanced activity when compared with the corresponding unsubstituted compound of Example 21 of the '994 application (as also shown above).

The Office Action at page 5, however, states that Applicants should have also compared the compound of their Example 6 with the compound of Example 2 of the '994 application (each as shown above). Therefore, Applicants now submit a second Declaration of Dr. Wachendorff-Neumann showing that the N-methylated compound of their Example 6 exhibits unexpectedly enhanced activity against *Sphaerotheca fuliginea* when compared with the corresponding unsubstituted compound of Example 21 of the '994 application. In particular, Applicants' inventive compound when sprayed on cucumbers was noticeably more protective than the known compound and when applied systemically to cucumbers (i.e., via the growth medium) exhibited a 100% protective effect using an application rate at which the known compound was entirely ineffective.

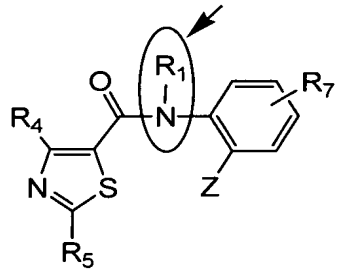
Applicants therefore respectfully maintain that their claimed invention is patentably distinct from the '994 application and that a terminal disclaimer is thus not needed.

Rejection under 35 U.S.C. 103

Claims 18-25, 27, and 29-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/059086 ("Walter et al") and CA 2,474,902 ("Elbe et al"), each taken alone or in combination with each other and each in further combination with JP 08/176112 ("Kanji et al"). Applicants again note that Walter et al is a counterpart of published US 2004/0138265 and that Elbe et al is a Canadian counterpart of the '994 application (which was discussed above with respect to double patenting). Applicants again respectfully traverse.

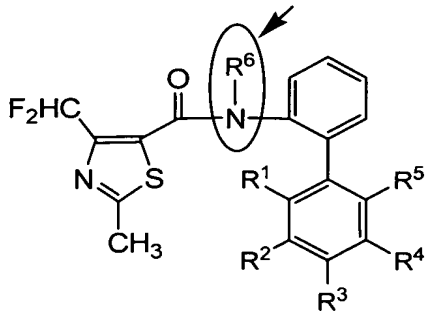
As discussed above with respect to the obviousness-type double patenting rejection based on the counterpart U.S. '994 application, **Elbe et al** discloses carboxamides in which the bridging amide nitrogen atom is never N-substituted, whereas the compounds of Applicants' invention must be N-substituted. Thus, for essentially the reasons discussed above with respect to the double-patenting rejection, Applicants submit that Elbe et al would not itself lead those skilled in the art to their claimed invention. Applicants further submit that Elbe et al, even when taken with Walter et al, would not lead those skilled in the art any closer to their claimed invention than what is already disclosed in Walters et al.

As Applicants have fully discussed in previous Amendments, **Walter et al** discloses certain microbicidal carboxamides, among which (as selected from among a very large array of possibilities) are compounds represented by the formula



(which is not shown as such in the reference but is pieced together from the general disclosure) in which $\mathbf{R_1}$ is CH–C≡C-R_2, $CH_2CH{=}CHR_2$, $CH{=}C{=}CHR_2$, or COR_3; $\mathbf{R_2}$ is hydrogen or one of several carbon-containing substituents; $\mathbf{R_3}$ is optionally substituted C_1-C_6alkyl (in which the optional substituent is halogen, C_1-C_6alkoxy, or C_1-C_6haloalkoxy) or is C_1-C_6alkylthio, C_1-C_6haloalkylthio, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkenyloxy, C_3-C_6haloalkenyloxy, C_3-C_6alkynyloxy, or C_3-C_6haloalkynyloxy; $\mathbf{R_4}$ is methyl that is optionally fluorinated (including, among others, CF_2H) or is chlorine or bromine; $\mathbf{R_5}$ is methyl or one of three other narrowly defined groups; and **Z** is phenyl or halophenyl, optionally substituted C_5-C_7 cycloalkyl, or a branched alkyl group. See Applicants' previous Amendment. As previously pointed out, Walter et al thus discloses compounds in which the bridging amide group (shown by the oval and arrow above) can be substituted with either (1) an unsaturated hydrocarbon group having at least one carbon-carbon multiple bond or (2) a carbonyl group connected to a narrowly defined set of optionally substituted alkyl, alkoxy, alkylthio, alkenyloxy, or alkynyloxy groups (i.e., COR_3).

Applicants, on the other hand, claim thiazolylbiphenylamides of formula (I)



(I)

in which the bridging amide nitrogen atom (again shown by the oval and arrow above) is substituted by either (1) non-carbonyl R^6 groups that are entirely different from the unsaturated hydrocarbon groups taught by Walter et al or (2) certain carbonyl-containing R^6 groups. For the purpose of simplifying their somewhat complex arguments, Applicants will address each type of substitution separately. Since the Office Action relies on Walter et al taken alone or in combination with Elbe et al (as well as Kanji et al) as it relates to what one would expect for unsubstituted amides vs. N-substituted amides and since Walter et al does not exemplify compounds having simple N-alkyl substituents (such as methyl) or N-alkenyl substituents (such as found in compound 7.03 of Walter et al) in conjunction with CHF_2-substituted thiazole rings, Applicants must rely on the two Declarations of Dr. Wachendorff-Neumann, even though part of the first Declaration and all of the second Declaration include comparisons based on examples taken from Elbe et al.

First, with respect to compounds of Applicants' invention in which the amide substituent is not a carbonyl group, Applicants again point out that such compounds are not taught or suggested by Walter et al and thus maintain – even without reference to Dr. Wachendorff-Neumann's Declarations – that Walter et al would not lead those skilled in the art to such compounds. Applicants' Claim 29 is one example of a claim directed to such nonobvious compounds having such "non-carbonyl" substituents. For these compounds, Dr. Wachendorff-Neumann's newly submitted second Declaration shows that the N-methyl compound of their Example 6 exhibits unexpectedly enhanced activity against *Sphaerotheca fuliginea* when compared with the corresponding unsubstituted compound of Example 21 of the '994 application. More particular, spray application of Applicants' inventive compound onto cucumbers provided noticeably more protection spray application of the known compound and,

even more dramatically, systemic application Applicants' inventive compound to cucumbers via the growth medium provided a 100% protective effect at an application rate at which the known comparative compound was entirely ineffective.

Applicants acknowledge that Walter et al does disclose certain N-alkenyl substituted compounds (which also are not carbonyl substituted), such as the compound 7.03 mentioned in the Office Action at page 9. However, Walter et al the only N-alkenyl substituted compounds specifically disclosed in Walter et al also have a trifluoromethyl-substituted thiazole ring instead of a difluoromethyl-substituted thiazole ring as required by Applicants. Since Applicants have shown – as discussed below with respect to carbonyl-substituted amides – that difluoromethyl substitution in the thiazole ring is associated with enhanced activity relative to trifluoromethyl substitution, it is reasonable to conclude that those skilled in the art would not be led from compounds such as compound 7.03 to the compounds claimed by Applicants.

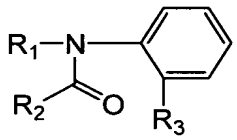
Second, with respect to compounds of Applicants' invention in which the amide substituent is a carbonyl group, Applicants maintain that such compounds are also patentably nonobvious over Walter et al. [Applicants note at the outset in this respect that the Office Action has indicated that the Office Action has indicated that Claims 27 and 28, which are directed to narrowly defined carbonyl-substituted amide compounds, would be allowable if written in proper independent form.] Applicants again acknowledge that the amide substituent group R^6 of their claimed compounds includes carbonyl groups that are in some cases similar to the carbonyl group COR_3 of the reference. For example, among the many meanings of R_1 of the reference can be found a carbonyl group COR_3 in which R_3 is an optionally substituted alkyl group or a (halo)alkoxy group. However, the teachings of Walter et al must be viewed in proper context. As mentioned above with respect to "non-carbonyl" compounds and as pointed out in Applicants' previous Amendment, Walter et al does not describe the particular combination of structural features that characterize the carbonyl-containing embodiments of Applicants' claimed invention nor does the reference show even one example of a N-carbonyl-substituted compound in which A is a thiazole and R_4 is a group other than CF_3. Only by picking and choosing from the host of possible groups disclosed in the reference could one arrive at Applicants' specified combination of features. [As Applicants have previously pointed out, one would need to select from among five heterocyclic structures of from group A only

thiazoles (A3), from among six ring structures of for group Q only certain substituted phenyl groups (Q1) and (Q6), from among several possibilities of group R_4 only CF_2H, and from among the seven possibilities of group R_1 only COR_3, and even then with only some of the substituents R_3.] Although Applicants believe that this failure to disclose specific compounds within the scope of their claims is consistent with the patentability of their invention, Applicants provided data in the first Declaration of Dr. Wachendorff-Neumann showing that their compound of Example 9 – which has both an N-carbonyl amide substituent and a difluoromethyl substituent in the thiazole moiety – provided significantly enhanced biological activities than the comparison compound of Example 4.32 of Walter et al (see page 33) – which has the same N-carbonyl amide substituent but has a trifluoromethyl substituent in the thiazole moiety. Applicants therefore maintain that their claimed N-carbonyl-substituted compounds are patentable over Walter et al.

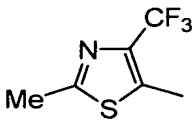
Applicants note by way of comment the reference in the Office Action at page 9 to the compound of Example 4.19 of Walter et al, which differs from the compound of Example 4.32 only in having an N-acetyl amide substituent instead of a methoxyacetyl substituent. Since Applicants have already carried out a directly comparative experiment showing the significance of difluoromethyl substitution in the thiazole moiety, Applicants fail to see why another test using compound 4.19 of the reference would not be essentially duplicative and unnecessary.

Applicants therefore submit that their claimed invention is patentably distinct from Elbe et al and Walter et al, whether taken alone or together.

Applicants maintain that Kanji et al would not lead those skilled in the art to their claimed invention. As Applicants have already discussed in their previous Amendments, **Kanji et al** discloses carboxamides of the formula



in which $\mathbf{R_1}$ can be any number of groups, including acyl groups of formulas -CO-R_4 (where R_4 can be alkyl, haloalkyl, or phenoxymethyl) or a second amide moiety -CO-NH-R_5 (where R_5 can be alkyl or phenyl), as well as certain ethers R_6 or alkyl groups R_7; $\mathbf{R_2}$ can be a variety of cyclic groups, including a specific trifluoromethyl-

substituted thiazole moiety having the formula 

; and R_3 can be any of a variety of cyclic or unsaturated groups, including phenyl. The Office Action relies on Kanji et al as teaching the interchangeability of substituents at the amide nitrogen atom. See Office Action at pages 10 and 14. However, even if this reference is read as broadly as the Office Action insists, Applicants maintain that reliance on the asserted interchangeability of amide substituents is insufficient to rebut the validity of their test results showing that the particular combination of features that characterize their invention – including not just N-substitution but also difluoromethyl substitution in the thiazole moiety – give rise to unexpectedly enhanced activities compared to the compounds taught by the various references.

Applicants therefore respectfully submit that their claimed invention is not rendered obvious by Walter et al and Elbe et al, whether taken alone or in combination with each other or in further combination with Kanji et al.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

Respectfully submitted,

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